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FLUORESCENT MICROSCOPY OF THE HUMAN SKIN.

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FLUORESCENT MICROSCOPY OF FIXED TISSUE.

Fluorescent microscopy has been widely used in the biological field ; Ellinger (1940) gave a good review of the subject with a comprehensive bibliography. Metcalf and Patton (1944) described the apparatus for fluorescent microscopy and published a list of fluorochromes with recommendations for their particular uses. Natural fluorescence of vitamin A in the skin was reported by Cornbleet and Popper (1942) who also in 1943 described the characteristic fluorescence of a paraffinoma. More recently, Van Duijn (1954) reported his findings with untreated and " fluorochromed " biological tissues. Sulzberger *et al.* (1954) employed fluorochromes for the demonstration of sweat ducts in the epidermis.

The present work was undertaken not to localize any particular chemical or tissue, but rather to use this method as a staining technique additional to the usual methods applied to skin biopsies.

Apparatus.

Our first attempts were carried out with a Hanovia fluorescent lamp of 240 watts output, fitted with a Wood's glass filter. A second filter of 5% copper sulphate solution acidified with sulphuric acid was interposed between the light

source and the microscope mirror. An ordinary microscope with glass objectives, eyepiece, and a sub-stage condenser was employed : it was found that the standard glass mirror was suitable for use with this wave-length of light. A third filter, a Leitz " Euphos ", was placed in the eyepiece of the microscope.

The Wood's filter allowed the transmission of light in the wave-length range of 3600–4000 Ångström units, and also some visible and infra-red rays : the latter was removed by the copper sulphate solution filter. The " Euphos " filter in the eyepiece prevented any stray ultra-violet rays from reaching the observer's eye, as it did not allow the transmission of rays below 4000 Å.

With this simple apparatus it was found possible to carry out preliminary studies with a series of fluorochromes. For fluorochromes giving only a weak fluorescence, a quartz sub-stage condenser is required, and an aluminized mirror is preferable to the standard glass one, as less of the exciting radiation is lost at the reflecting surface.

It is important to have an adequately powerful source of ultra-violet rays. The less powerful sources having an output of 100–150 watts are of use only with the more brilliant fluorochromes.

Technique.

Fixation and processing of tissue.

Biopsies of normal skin approximately 2 mm. in thickness were fixed in 70% alcohol for at least 18 hours. The tissue was then dehydrated by immersion in 98% alcohol for three hours and then in two changes of absolute alcohol (the first for two hours and the second for three hours). Clearing was effected by overnight treatment with cedar-wood oil ; the excess oil was removed by placing the specimen in benzene for thirty minutes. Next the biopsies were impregnated with two changes of paraffin wax (melting point 58° C.) in an oven at 60° C. for $4\frac{1}{2}$ hours.

An alternative method of clearing, which did not interfere with the fluorescence of the sections, was the use of 1% celloidin in methyl benzoate : this solution was changed three times in $2\frac{1}{2}$ days.

Sections were cut at 5μ and floated on to ordinary thin glass slides previously treated with glycerine egg albumin. They were then dried overnight in an incubator at 37° C. Prior to staining the sections were placed in xylol for at least 15 minutes, rinsed in graded alcohols of decreasing concentration, and finally washed in distilled water.

Staining.—Thirty-five fluorochromes and combinations of fluorochromes have been studied with normal skin. With two exceptions, all were used in aqueous solution, in a dilution of 1 in 1000. Fluorescein is insoluble in water and was therefore dissolved in 60% alcohol to the above strength. Primulin was used in a dilution of 1 in 10000 in addition to the usual concentration ;

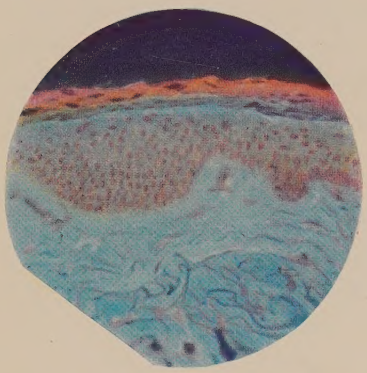

Fig. 1.—Normal skin. Acridine orange and primulin. Epidermal keratin, orange; stratum granulosum, green; nuclei, red; collagen, blue.

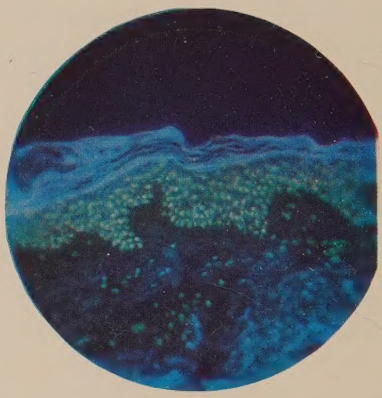

Fig. 2.—Normal skin. Thioflavine T and thioflavine S. Epidermal keratin, blue; nuclei, yellow; collagen, blue.

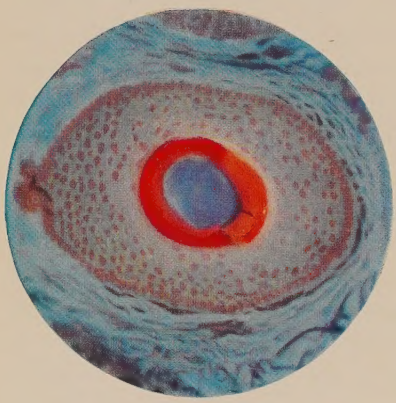

Fig. 3.—Normal hair follicle. Acridine orange and primulin. Inner root sheath, brilliant red; nuclei, red, collagen, blue; hair, bright blue.

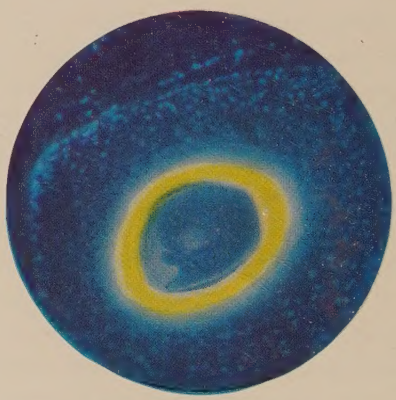

Fig. 4.—Normal hair follicle. Thioflavine T and thioflavine S. Inner root sheath, brilliant yellow; nuclei, yellow; hair, blue.

with this weaker solution, the staining time was prolonged to twenty-four hours.

In the case of all the other fluorochromes the staining time was three minutes. With combinations of more than one fluorochrome, each fluorochrome was allowed to act for three minutes, the section being washed with distilled water after each. After washing, the sections were rapidly taken through 98% alcohol and absolute alcohol to xylol. They were then mounted in Gurr's " DePeX "; canada balsam is not suitable for this work as it is fluorescent.

Results.

The colours given by various structures of the skin when treated with a variety of fluorochromes and fluorochrome combinations are shown in Tables I and II. It will be seen that some fluorochromes are useless when examined by light of the wavelength afforded by the present apparatus : this however does not imply that they cannot be excited by rays of a different wave-length.

With combinations of acridine orange and primulin (Figs. 1 and 3) and also with thioflavine S and thioflavine T (Figs. 2 and 4), the tissue differentiation is excellent. This allows the detailed structure of the skin to be studied at high magnifications with oil immersion objectives. Sandalwood oil is used instead of cedar wood oil for immersion work as the latter has quite a strong fluorescence.

These methods can reveal differences in keratin that are not detectable by ordinary techniques. Thus, epidermal keratin gives an orange colour with acridine orange and primulin, while the keratin of the inner root sheath of the hair follicle has a brilliant red fluorescence and the hair itself is blue (Fig. 3). With thioflavine S and thioflavine T, the inner root sheath fluoresces a brilliant yellow and epidermal keratin is blue (Figs. 2 and 4).

FLUORESCENT MICROSCOPY OF FRESH TISSUE.

Because of the changes inevitably induced in tissue by any method of fixation it was thought worth while to investigate the use of fluorochromes on fresh material. Immediately after removal the biopsy was placed in saline-soaked gauze and surrounded with ice. The specimen was then left in a cold room at a temperature of about + 4° C. until required.

The tissue was processed within twenty-four hours of removal. Sections about 15μ thick were cut with a freezing microtome and immediately placed in a cooled fluorochrome solution at about + 3° C. The fluorochrome was run into the staining chamber from an aspirator bottle, through a spiral immersed in a freezing mixture of salt and ice. The chamber was kept cool by a jacket containing ice and water. The fluorochrome solution was kept in circulation by a siphon which allowed it to flow into a receiver. The fluorochrome was then returned to the aspirator bottle at appropriate intervals.

TABLE I.

Fluorochrome.	Cytoplasm of epidermis and appendages.	Nuclei of epidermis, appendages, and leucocytes.	Collagen.	Keratin.			Notes.
				Epidermal.	Root sheath.	Hair.	
Primulin 0·01%	Greenish yellow	Grey	Blue-grey	Light blue	Light blue	Blue	Strong fluorescence. Reasonable differentiation.
Acridine orange 0·1%	Green	Red	Blue-green	Orange	Red	Blue	Str. granulosum green. Differentiation good.
Acridine yellow 0·1%	Light brown	Bright yellow. Leucocyte nuclei orange	Dark blue	Blue green	Yellow	Blue	Good nuclear fluorescence.
Acridine red 0·1%	Purple	Pale red	Blue	Blue	Blue	Yellow	Fluorescence not brilliant.
Thioflavine S 0·1%	Grey	Pale yellow	Bright blue	Bright blue	Brilliant blue	Blue	Poor differentiation. Good collagen stain.
Thioflavine T 0·1%	Light brown	Yellow	Dark blue	Light blue	Yellow	Blue	Excellent nuclear stain. Elastic tissue blue-yellow.
Rhodamine 3 G.O. 0·1%	Blue	Orange	Blue	Yellow	Brick red	Yellow	Reasonable differentiation.
Eosin and haematoxylin	Dull red	Dull blue	Golden yellow	Golden yellow	Yellow	Blue	Good collagen and keratin fluorescence.
Magdala red	Brown	Non-fluorescent	Yellow-orange	Orange	Yellow	Blue	Poor differentiation.
Titian yellow	Dark yellow	Non-fluorescent	Blue	Blue	Blue	Blue	Granular layer yellow. Poor differentiation.
Euchrysine 0·1%	Green	Red	Green-blue	Orange	Red	Blue	Identical with fluorescence with Acridine orange.
Acid alizarin blue 0·1%	—	—	Very poor red-blue fluorescence	—	—	—	Of no value.

Coriphosphine 0·1%	Dark green	Dark orange	Blue and green	Green-orange	—	Orange	Reasonably good differentiation. Fluorescence not brilliant.
Brilliant dianil green G 0·1%	Dark blue	Non-fluorescent	Blue	Light blue	—	Blue	Poor differentiation.
Fluorescein (alc. sol) 0·1%	Grey. Non-fluorescent	Non-fluorescent	Brilliant lime green	Lime green	Light green	Green	Good collagen fluorescence.
Uranin (water sol.) 0·1%	Non-fluorescent	Non-fluorescent	Lime green	Green	Blue	Non-fluorescent	Collagen stain only.
Rhodamine B 0·1%	Blue	Pink	Purple	Bright orange-yellow	Orange	Brown	Good nuclear fluorescence. Poor differentiation.
Rhubarb extract 0·1%	—	—	—	—	—	—	Of no value.
Thioflavine S and thioflavine T	Dark yellow	Bright yellow	Bright blue	Pale blue	Brilliant yellow	Blue	Very good differentiation, showing nuclear detail, collagen and keratin (Figs. 2 and 4).
Primulin and acridine orange	Pale green	Red	Light blue	Orange	Red	Blue	Excellent differentiation (Figs. 1 and 3).
Primulin and thioflavine T	Grey	Light yellow	Bright blue	Pale blue	Yellow	Blue	Fair differentiation, not quite as good as Thioflavine S and T (double stain).
Thioflavine S and rhodamine 3, G.O.	Pale green	Light pink	Blue	Pale pink	Pale pink	Blue	Good nuclear and collagen fluorescence.
Thioflavine S and euchrysine	Green	Red	Blue	Orange	Yellow and orange	Blue	Str. granulosum yellow. Very good differentiation. Muscle orange-green.
Thioflavine S and acriflavine	Dark yellow	Brown	Brilliant light blue	Light blue	Bright blue	Pale blue	Differentiation not satisfactory.
Fluorescein and acridine orange	Dark green	Red	Deep lime green	Orange	Red	Blue	Good collagen fluorescence.
Berberin sulphate 0·1%	Grey	Brilliant green	Dark blue	Blue	Brilliant green	Grey	Excellent nuclear fluorescence.

Table II.

Fat Fluorescence.

(Formalin fixed, frozen sections).

Fluorochrome.	*Colour of Fat Fluorescence.*
Magdala Red . . .	Blue
Titian yellow . . .	Blue
Phosphine	Light blue
Rhodamine B. . . .	Blue

After the sections had been in the fluorochrome solution for about five minutes they were washed in normal saline. The saline, contained in another aspirator bottle, was run through the same spiral as the fluorochrome into the staining chamber. This change over to saline was accomplished by means of a two-way tap connecting the two aspirator bottles.

When the sections had been washed they were transferred to a cooled slide, mounted in saline, and examined on a cooled microscope stage with the filtered exciting radiation previously described.

The cooled microscope stage consisted of a rectangular brass box, 4·5 cm. by 9·0 cm. by 0·8 cm., with a central hole 1·2 cm. in diameter to allow the exciting radiation to reach the section. An inflow tube permitted the passage through the cooling chamber of water which had been cooled by a freezing mixture of salt and ice ; the outflow tube was connected to waste. With this arrangement it was possible to maintain the section at reasonably low temperatures during observation. If, however, the sections were to be examined for only a short time the cooled stage was not employed.

With this technique, using an aqueous solution of acridine orange 1 in 10,000, it was found that the epidermal cell nuclei and the nuclei of leucocytes fluoresced green, instead of red as they do in alcohol-fixed tissue. The collagen was light blue, and delicate yellow strands of elastic tissue could be seen running through the collagen. The larger medullated nerve fibres could be detected, and the fat in the sebaceous glands fluoresced a silvery-blue. This method therefore enables one to examine the skin without any distortion due to fixation and processing, and at the same time the intra-vital fluorochrome gives a tissue differentiation equal to if not better than routine histological techniques.

MICROPHOTOGRAPHY OF FLUORESCENT TISSUE

Apparatus.

The problems in the production of colour fluoro-micro-photographs have been considerable. The apparatus described below has proved to be the most efficient. With few exceptions we were unable to see the image on the ground glass screen ; it was therefore impossible to assess the exposure time or to focus the image.

An horizontal type of optical bench was employed; this obviated the need to change the direction either of the exciting radiation or of the projection of the image, and thus ensured a minimum loss of intensity.

The ultra-violet ray source was a Hanovia mercury vapour lamp of 240 watts output (Fig. 5). The radiation was passed through the same filtration as already described; a Wood's glass filter (F1) and a 5% copper sulphate solution

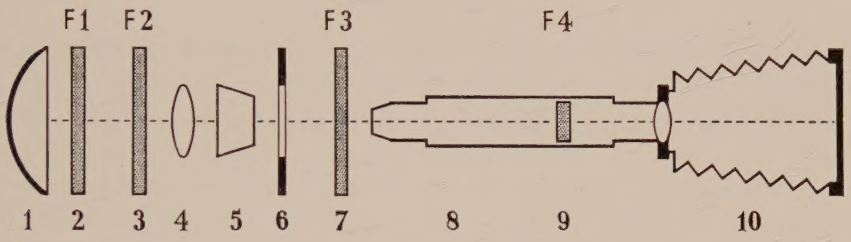

FIG. 5.—(1) U.V. source. (2) Wood's glass filter (F1). (3) Copper sulphate solution filter (F2). (4) Quartz field condenser. (5) Quartz sub-stage condenser. (6) Section. (7) Wratten 2B filter (F3). (8) Microscope. (9) Colour correction filter CC 10 R (F4). (10) Camera.

(F2). The rays were concentrated by a quartz field condenser and then passed through the quartz sub-stage condenser to the section. A Wratten 2B gelatine filter was interposed between the coverslip of the section and the microscope objective (F3) in order to remove the excess ultra-violet rays. In the barrel of the microscope (M) a Wratten CC 10 R colour correction filter (F4) was inserted. An ordinary camera, without a lens, was attached by a light-tight collar to the ocular of the microscope.

Factors governing the source of radiation were high energy emission with a uniform intensity during long exposure times. For these reasons it was found that neither a carbon arc nor a low output mercury vapour lamp were suitable.

The choice of filters was made from a purely practical standpoint; this applied particularly to filter 3. From several filters chosen by us from manufacturers' absorption curves, only the Wratten 2B was found to intercept sufficient ultra-violet rays to prevent fogging of the photograph. For convenience a Leitz "Euphos" ocular filter was used for visual work, but this must be changed for the Wratten 2B before the apparatus is used for photography: otherwise the colour rendering is distorted. It must be remembered that any filtration through coloured filters may alter the character, contrast, and colour of the image: also some of the dyes used in filters are themselves fluorescent and therefore cannot be used.

We found that $\frac{1}{6}$ in. objectives with a N.A. of 0·70 or higher caused considerable flare and had to be discarded. A projection eyepiece was usually employed, but satisfactory results were obtained with standard oculars.

The choice of colour materials, at the time of writing, has not been fully

investigated by us, but satisfactory results have been obtained on Ektachrome sheet film type " A ". With some sections, however, the colour rendering was completely lost owing to low-intensity reciprocity failure, and we believe the bottom layer of emulsion was not excited. Further work is being undertaken, particularly on negative-positive material, with a view to overcoming this difficulty.

Method.

Illumination.—The most satisfactory was found to be Köhler illumination.

Focussing.—With a few of the more brilliant fluorochromes an image could be focussed on to the ground-glass screen. In other cases the focussing was adjusted in visible light ; this was effected by placing an electric light bulb between the field and sub-stage condensers. Rarely, with some fluorochromes that were colourless in visible light, a trial and error method had to be adopted. The image was focussed visually by the observer looking down the microscope, the camera was then placed in position, and the fine adjustment turned back about 15° ; trial exposures on black and white material were then taken until a satisfactory focus was obtained.

Exposure.—Exposure times with colour material varied between nine minutes and twelve hours. In order to avoid undue waste, trial exposures in monochrome were taken.

An Ilford process panchromatic plate was exposed and developed to a gamma of 0·8 : the negative was checked for density, detail, and definition. The background, where there was no image, ideally had a density of 0·45. The initial length of exposure on panchromatic plates is dependent upon the type of apparatus, the intensity of the exciting radiation, and the particular fluorochrome employed.

When a satisfactory monochrome negative was obtained, its exposure time was multiplied by 4 ; this allowed for the difference between the emulsion speeds of the panchromatic and Ektachrome materials. A further factor was used to correct for low intensity reciprocity failure. This varied between 3 and $4\frac{1}{2}$, and depended on the initial exposure time of the black and white test. When this was less than one minute, a factor of 3 was used ; this factor was increased up to an initial exposure time of forty-five minutes. For all exposures of this duration and over, a factor of $4\frac{1}{2}$ was employed.

The Ektachrome film was then exposed for the calculated time ; the longer the time the less need there is for accuracy ; thus all exposures over six hours were taken to the nearest hour. Those exceeding ten hours are not recommended, as we found the intensity of the fluoroscence decreased during long exposures, and on several occasions the sections became spoiled. The copper sulphate solution boiled over during one long exposure, but if this is periodically checked, it can be replaced if necessary during the exposure.

Haematoxylin and eosin sections required excessively long exposure times, and consequently were greatly affected by low intensity reciprocity failure. The colour rendering was lost, and an all-over blue colour obtained instead of the yellow fluorescence due to eosin. These transparencies were copied by using a yellow-orange correction filter in order to restore the original colour values.

Summary.

The apparatus for fluorescent microscopy is described. The methods for processing tissue and for treating sections with fluorochromes are given in detail. The fluorescent colours obtained with a series of these substances on human skin are tabulated.

Vital staining of fresh tissue with acridine orange is mentioned. The apparatus employed, and the findings with normal skin are described.

Details of the photographic technique for the production of colour fluorophotomicrographs are reported.

We should like to express our thanks to Dr. W. N. Goldsmith for his help and encouragement with this investigation. Also we thank Mr. V. K. Asta, the medical artist of University College Hospital Medical School, for the illustration of the apparatus.

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THE HISTOPATHOLOGY OF EPIDEMIC FOLLICULAR KERATOSIS.

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An outbreak of epidemic follicular keratosis occurred in South Africa in 1954 and 1955. Forty-four cases were investigated and fully described by Craig Cochrane and Loewenthal (1955) and by Rudolph (1955). Many practitioners have reported further cases verbally, and one of us (L. J. A. L.) recently saw a case in Bulawayo, Southern Rhodesia.

Clinical Description.

The following account is reproduced (by permission) from the article by Craig Cochrane and Loewenthal (1955) :

Evolution.—The first lesions appear within 48 hours from the first constitutional symptoms in children; in adults they sometimes precede the constitutional symptoms. In many cases the first small macules appear on the thighs and forearms, in others on the central trunk. Within a very few hours the lesions become papular. During the first 72 hours the rash becomes more profuse over the trunk and proximal parts of the limbs, and scattered macular lesions are seen on the palms and soles. In some children the areas commonly affected by keratosis pilaris (and the phrynoderma of vitamin A deficiency) are markedly affected and the rash is then best seen and felt on the backs of the arms, buttocks and on the thighs, especially on the backs and outer sides. Fresh lesions do not, as a rule, appear after the third day. When fully developed, the rash is most profuse on the trunk, few lesions are seen below the knees, but the forearms show papules on all aspects. The face is affected to a varying degree : in none of our cases has it shown so profuse an eruption as on the trunk. In one patient the " side whisker " area was first affected by closely aggregated, follicular papules ; in others only a few scattered lesions were seen over the central area. When the scalp is affected the papules are sparse. The mucous membranes are not affected.

In the majority of patients there are no subjective symptoms, but a few children have experienced mild itching. On the palms a peculiar sensation, sometimes described as a " sore itch " has been reported.

Morphe.—The lesions appear first as macules ; except on the palms and soles, they become papular within 12 hours. These papules vary in diameter from 3-5 mm. and are often, during the first few days surrounded by a characteristic white halo about 5 mm. wide. The papules are pink to red in colour and often appear to be so tense as to be blanched on their summits, giving the impression of being vesicular. Puncture, however, does not lead to the escape of fluid.

From the third day onwards many of the papules, when examined under the loupe, show a tiny central spine or a minute, dark, comedo-like spot. When this change

affects a large number of lesions a "nutmeg grater" sensation is felt on stroking the area. During the second week, when the majority of lesions have subsided, faint staining is left and careful inspection shows prominent follicular "thorns" at the site of some, while others have developed larger, black, comedo-like centres. Both types are adherent, but on forcible removal some bring with them an imprisoned hair. In one case papules over the centre of the chest had coalesced to form an oval area about 1 inch in diameter, reminiscent of the type resembling granuloma annulare described by Schuppli.

Although many of the lesions are frankly follicular, this is not invariable, as is shown by those appearing on the palms and soles, where no pilo-sebaceous follicles exist.

Subsidence.—The papules flatten and fade from the sixth day: the macules on palms and soles have usually disappeared after a week. Many of the papules leave a faint brownish stain which, in most instances, disappears under diascopic pressure. The follicular spines and comedones, which appear prominently during the second week, persist for periods of up to 2 months. During the stage of subsidence the exanthem (which, during the first week, does not give the impression of being predominantly follicular) consists exclusively of follicular papules with a central spine or adherent comedo-like structure. These follicular lesions are by no means limited to the sites favoured by keratosis pilaris and may, indeed, spare these completely.

The cause of the disease was not discovered: bacteriological and a very few virological examinations were negative. The presence of atypical lymphocytes in blood smears, such as are often associated with a virus infection, might be of importance.

The method of spread of the epidemic was also obscure. Rudolph observed two instances of presumed infectious or contagious spread within families and their servants: Craig Cochrane and Loewenthal saw two cases in a household on one occasion only.

Histology.

Six biopsy specimens were examined: one was taken 24 hours after the first appearance of the rash, one on the 2nd day, two on the 4th day and two on the 7th day. Serial sections were cut at 4μ and stained with haematoxylin and eosin.

Case 1 (Fig. 1).—The biopsy specimen was taken 24 hours after the first appearance of the rash.

The epidermis shows minimal changes in the form of intracellular oedema of an occasional prickle cell and invasion by a few lymphocytes. The mouth of one follicle is somewhat dilated and plugged with keratin. At the rim of this follicle there is a very small focus of parakeratosis. The two sweat ducts present in the specimen show well-marked intracellular oedema in their intra-epidermal portion only. In the upper and mid-dermis there is a perivascular infiltrate consisting mainly of lymphocytes with some histiocytes, more pronounced in the vicinity of the follicles and sweat ducts. In addition there is a very sparse diffuse infiltrate in the upper dermis consisting of histiocytes, lymphocytes and a few polymorphonuclear leucocytes. The blood vessels in the main show no alteration, but a few capillaries show some swelling of their endothelial cells.

The most significant feature is the presence around the dilated follicle of a recent extravasation of red blood cells which lie closely apposed to the follicle in a narrow

band about 50μ in width. The haemorrhage extends on all sides of the follicle up to the epidermis and laterally for a short distance on either side below the epidermis Within the area of the haemorrhage there is no noticeable increase in the inflammatory cell infiltrate. Search through serial sections revealed no other haemorrhages and Perl's stain for haemosiderin was negative.

Fig. 1.—Case 1. 24 hours. × 100. H. & E. Surrounding the follicle there is a band of extravasated red blood cells and in the upper and mid dermis there is a perivascular infiltrate.

Case 2.—The biopsy specimen was taken 2 days after the appearance of the rash. The epidermis shows no abnormality apart from slight hyperkeratosis of the basket-weave type. Associated with a hair follicle and most marked in its middle third, there is a dense infiltrate of lymphocytes and histiocytes. Other follicles in the specimen are free of infiltrate, but in the vicinity of one there is a recent extravasation of red blood cells which extends also around a neighbouring eccrine sweat gland. Haemosiderin is not present. Surrounding another sweat gland there is a scanty lymphocytic and histiocytic infiltrate. In the upper and mid dermis there is a perivascular infiltrate consisting mainly of lymphocytes with some histiocytes. The most significant feature is the change in the blood vessels. Their endothelial cells are swollen and their walls are thickened and oedematous.

Case 3 (Fig. 2).—A biopsy specimen taken on the fourth day of the rash shows the following features. The epidermis shows some hyperkeratosis and foci of acanthosis. In one or two areas the basal cells show hydropic degeneration and the epidermo-dermal junction is blurred. The papillae are markedly oedematous and in two separate areas the oedema fluid extends into the epidermis disrupting the rete Malpighii and forming a small vesicle containing a few polymorphonuclear leucocytes. These papillae and the subjacent upper dermis are diffusely infiltrated by histiocytes, lymphocytes and occasional polymorphonuclear leucocytes. There are also a few extravasated red blood cells. In the upper and mid dermis there is a well-marked perivascular infiltrate consisting of lymphocytes, histiocytes and scanty eosinophils. The blood vessels show swelling of their endothelial cells and some show thickening and oedema of their walls. One vessel is thrombosed : its wall shows fibrinoid degeneration and is infiltrated by a few lymphocytes.

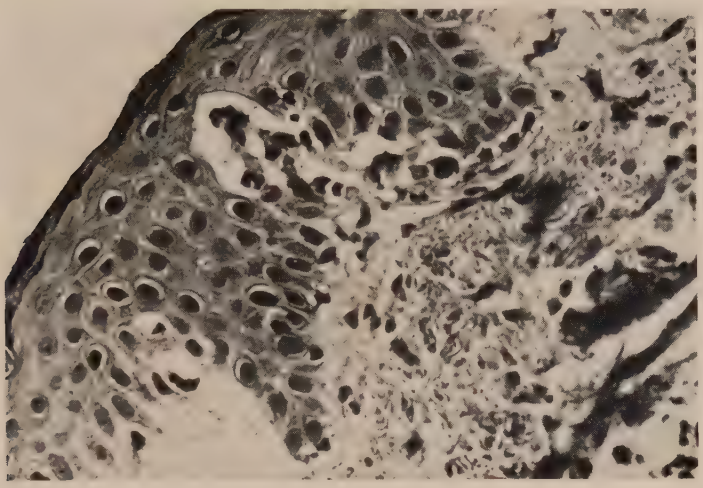

FIG. 2.—Case 3. 4th day. × 400. H. & E. The papillae are oedematous. The oedema fluid has disrupted the overlying epidermis and produced a small vesicle which contains a few inflammatory cells.

CASE 4.—This biopsy specimen was also taken on the fourth day of the rash. It shows no significant change in the epidermis. In the dermis the blood vessels are dilated and there is a perivascular infiltrate consisting of lymphocytes and histiocytes. The endothelial cells of the blood vessels are swollen and their walls are slightly thickened. The most noticeable feature is the presence of an infiltrate around the sweat glands consisting of polymorphonuclear leucocytes, histiocytes and a few lymphocytes. A similar but less intense infiltrate is present around some of the hair follicles.

CASE 5. (Fig. 3). —This biopsy specimen was taken about 7 days after the appearance of the rash. There is a sharply demarcated area surrounding a hair follicle in which the epidermis is degenerated—the prickle cells stain intensely eosinophile and their nuclei are pyknotic. In parts the epidermis has separated from the dermis. Immediately

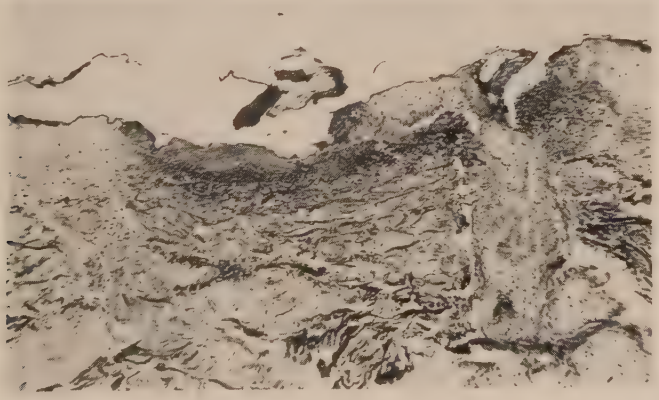

FIG. 3. Case 5. 7th day. × 50. H. & E. There is a small superficial infarct in the vicinity of a hair follicle.

below this the dermis is necrotic and almost completely devoid of cells. Beneath the necrotic area there is a band-like infiltrate consisting of polymorphonuclear leucocytes, nuclear debris and a few red cells. A blood vessel below this lesion shows marked swelling of its endothelial cells, thickening and oedema of its wall and early thrombus formation. It is surrounded by an infiltrate consisting of histiocytes, a few lymphocytes and polymorphonuclear leucocytes and one or two eosinophils. The epidermis surrounding this lesion is spongiotic and the papillae are oedematous. In the centre of the lesion there is an island of relatively normal epidermis surrounding the mouth of the follicle. The histological features are those of a small infarct.

In addition there is a second smaller lesion adjacent to the main one. It consists of a small subepidermal vesicle containing a few polymorphonuclear leucocytes. The overlying epithelium is degenerated. The subjacent dermis is infiltrated by a few polymorphonuclear leucocytes. Deep to this there is a blood vessel showing swelling of its endothelial cells, thickening and oedema of its wall and a perivascular infiltrate consisting of a moderate number of polymorphonuclear leucocytes, histiocytes, lymphocytes and a very occasional eosinophil. Other blood vessels in the upper and mid dermis are similarly affected and one sweat duct is surrounded by a similar infiltrate.

Case 6 (Fig. 4).—This biopsy specimen was taken from Case 1 on the 7th day of the rash and included a comedo-like lesion. The epidermis shows hyperkeratosis as compared with the previous biopsy, an increase in the granular layer and slight

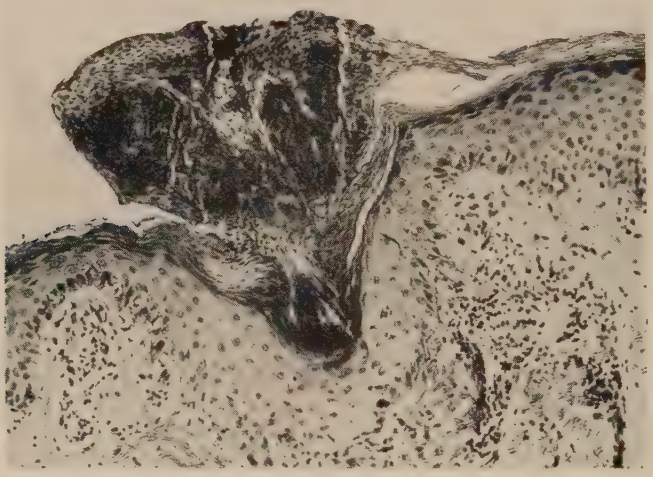

Fig. 4.—Case 6. 7th day. × 130. H. & E. Comedo-like lesion.

acanthosis. A few of the basal cells show intracellular oedema and the subjacent papillae show slight oedema. There is one dilated follicle, around the mouth of which and extending downwards for some distance into it the stratum corneum is parakeratotic. Protruding from this follicle there is a conical mass with its apex in the follicle and its base directed to the surface. Its superficial aspect consists of parakeratotic stratum corneum which is continuous with the stratum corneum of the epidermis. The sides of the cone consist of the parakeratotic lining of the mouth of the follicle. The central core of the mass is composed of keratin embedded in which there is a dense conglomeration of unrecognizable nuclear debris. The prickle cells

of the follicle are swollen and stain less intensely than the epidermal prickle cells. Surrounding the follicle there is some oedema with blurring of the epidermo-dermal junction.

In the upper and mid dermis there is a perivascular infiltrate consisting of lymphocytes and histiocytes. It is most marked in the vicinity of the affected follicle. The endothelial cells of the blood vessels are swollen and their walls are slightly thickened. The lymphatic vessels are dilated. Haemosiderin was not detected by Perl's stain.

The histopathological changes observed in these six specimens may be summarized as follows ;

The earliest changes, appearing in the first 24 hours, are congestion and the development of a perivascular infiltrate consisting of lymphocytes and histiocytes. The endothelial cells of some of the blood vessels become swollen. Extravasation of red blood cells may occur even during the first day, or the vessel may thrombose. Within the next two days all the blood vessels in the upper and mid dermis show marked swelling of their endothelial cells and their walls are thickened and oedematous. Some of them show fibrinoid necrosis and the vessel wall may be infiltrated by inflammatory cells. At this stage a few polymorphonuclear leucocytes and sometimes eosinophils appear in the infiltrate.

Presumably as a result of the vascular changes the upper dermis becomes oedematous and there is interference with the nutrition of the overlying epidermis. The oedema fluid disrupts the degenerated epidermis. Small haemorrhages may occur, and thrombosis may even result in infarcts.

The perivascular infiltrate appears to be most pronounced in the vicinity of the hair follicle and sweat glands. In addition there is a diffuse inflammatory infiltrate around these adnexae. The cells lining the intra-epidermal portion of the sweat ducts are oedematous.

The inflammation and haemorrhage around the hair follicles apparently interferes in some way with the normal process of keratinization and results in parakeratosis. The usual effect of this is failure to shed keratin. Parakeratotic material therefore accumulates in the mouth of the follicle, producing the characteristic horny mass from which the disease derives its name of follicular keratosis.

The basic pathological processes are therefore an angiitis and an inflammation of the skin adnexae. The end results depend on the severity and situation of the lesion. The angiitis may produce oedema and vesiculation, small haemorrhages or infarcts. The perifolliculitis and haemorrhage around the follicles produce the horny spine or comedo-like structure.

Discussion.

Of previously reported outbreaks, that described by Bowers (1952) in Cheltenham most closely resembles the present epidemic. That of Schuppli

(1947) in Basle differs in several important clinical features from either : these differences have been tabulated by Craig Cochrane and Loewenthal (1955).

Histologically, too, we feel that there are fundamental differences between our findings and those reported by the above authors, which are briefly summarized here ;

(*a*) Schuppli (1947) described three types of case, of which by far the commonest was a slowly evolving eruption resembling acne. In this type the principal change was hyperkeratosis of the follicular epithelium affecting every follicle and leading, in those most severely affected, to the development of horn cysts. He noted that inflammatory infiltrates were usually absent from the neighbourhood of the follicles and that they did not occur around the blood vessels. The other types, briefly described, showed variations of the above picture, including acanthosis ; there is no mention of changes in or around the blood vessels.

(*b*) Bowers (1952), in what was admittedly a preliminary report, gave the histological findings in his epidemic as follows :

" Sections taken from 2 patients on the second and third days of the rash respectively, show collagenous oedema, maximal around the follicles in one patient, but generalized in the other.

" Dr. Ian Whimster commented that the appearance was that of an urticaria and suggested that it might be due to an antigen entering the skin through the follicles. He thought that the horny plugging noted in the later stages of the eruption was secondary to the perifollicular oedema.

" Dr. Alastair Dudgeon kindly stained and examined some sections for me, and did not think that the appearance was compatible with a virus infection."

Our findings seem to be entirely different from those quoted in (*a*) and (*b*). Neither Schuppli nor Bowers mentions the prominent perivascular infiltrate or the severe vascular changes followed by haemorrhage or thrombosis and their sequelae. These profound histological differences, added to those already noted in the clinical picture, make us believe that the South African epidemic represents a disease distinct from those previously recorded.

The exact nature of the disease is still uncertain. Serological and cultural studies have so far proved negative : the histopathological changes do not provide the answer.

In measles and scarlet fever a perivascular infiltrate, swelling of the endothelial cells and sometimes extravasation of red blood cells occur. In both these diseases the lesion is often most marked in the vicinity of the dermal appendages. An angiitis with thrombosis and infarct formation is commonly seen in the typhus group of fevers.

The histopathological changes in the skin are therefore not specific. They are consistent with either a rickettsial or a viral infection localized in the walls of the blood vessels and skin appendages, or with an antigen-antibody reaction.

Summary.

1. The histopathological changes in six biopsy specimens from cases of epidemic follicular keratosis are recorded.

2. The basic pathological processes are an angiitis and an inflammation of the skin adnexae.

3. The angiitis may result in oedema and vesiculation, small haemorrhages or infarcts. The perifolliculitis or haemorrhage around the follicles leads to the formation of the horny spine or comedo-like lesion.

4. The histopathological changes in the skin are not specific. They are consistent with either a rickettsial or a viral infection localized in the walls of the blood vessels and skin appendages, or with an antigen-antibody reaction.

Acknowledgements.

Three of the specimens were submitted by Dr. J. Craig Cochrane of Vanderbijlpark and one by Dr. S. Gordon of Johannesburg. We are grateful for their permission to use their material in this publication. Mr. Ulrich of the South African Institute for Medical Research is responsible for the excellent microphotographs.

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OCULAR PEMPHIGUS WITH GENERALISED BULLOUS ERUPTION.

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Senior Registrar

AND

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In a previous paper (Church and Sneddon, 1953) we described the clinical features of ocular pemphigus as we had observed them in seven cases.

Skin lesions were present in only two of our cases and in neither was it possible to carry out histological studies. One of the patients (Case 4 in our previous paper) has been kept under observation and recently, after an interval of eight years, the skin lesions have recurred. We have been able to watch the development of a widespread bullous eruption and its regression with steroid therapy. Histological examination of a blister has on this occasion been possible.

In view of the findings which support the conception that ocular pemphigus is an entity distinct from pemphigus vulgaris, and the scarcity of reports on the histology of the skin in this disease, we considered it worth while reporting this single case in some detail.

Case History.

A housewife aged 70.

Eight years ago she developed soreness of the mouth and irritation of the vulva. Shortly afterwards blisters appeared on the labia majora, pubic and inguinal regions and these left extensive erosions after rupturing. A month later blisters appeared on the eyelids and there were recurrent attacks of epistaxis. During this time the patient felt unwell and lost weight.

In September 1947 she attended hospital. At that time she had small intact bullae and erosions on the left lower eyelid, the vulva and groins, and a blister on the tip of the tongue. She was admitted to hospital for treatment and six weeks later was discharged free from skin lesions but with pigmentation at the site of healed lesions which has persisted ever since. She complained of irritation of the eyes and excessive lachrymation, and the ophthalmologist (Mr. A. B. Nutt) reported that the right tear ducts were blocked by scar tissue. Apart from continued discomfort with the eyes she had no other mucosal lesions until May 1948, when she had more vulval irritation and superficial erosions were found.

In March 1950 she again attended hospital with conjunctivitis of the right eye and shrinkage of the conjunctiva was seen. Intact bullae were present on the buccal mucosa together with superficial erosions.

By November 1951 the eye lesions had progressed to the formation of adhesions in the right eye and conjunctival shrinkage was present in both eyes. The buccal lesions were still active and intact bullae were seen on the palate,

In January 1953 mucosal lesions again appeared on the vulva causing ulceration and the buccal ulceration continued to trouble her. By May 1954 the conjunctival adhesions had progressed so that the lower lids of both eyes were completely adherent, including the lateral and medial canthi. The upper lids were comparatively free. Adhesions had also formed between the left labia majora and minora and erosions were present around the vaginal orifice and perianal region. At that time she began using hydrocortisone eye ointment with diminution of the conjunctivitis.

In February 1955 a severe relapse of all the mucosal lesions was accompanied by a faint serpiginous-edged erythema extending over the groins and upper inner parts of the thighs in the area of pigmentation left by previous skin lesions. Mucosal and skin lesions all settled down after rest in hospital.

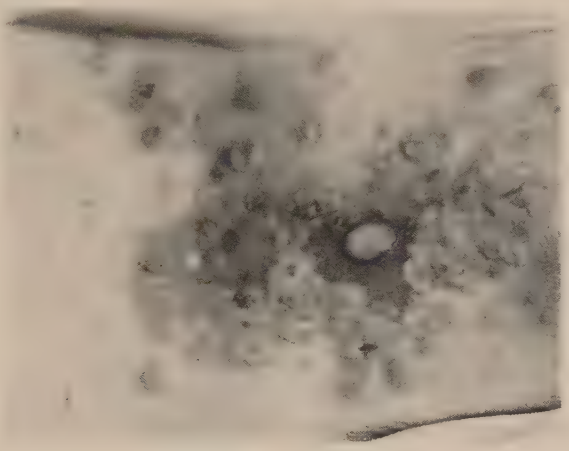

FIG. 1.

In August 1955 the mouth became very sore and eroded and a month later she developed a sudden crop of blisters on the trunk, axillae, and groins. On admission to hospital in September 1955 the eye lesions were aggravated by profuse purulent conjunctivitis: erosions of the whole buccal mucosa extended to the red margin of the lips and over most of the tongue, and there were scattered erosions over the palate. The mucosal lesions of the vulva and anus had also become extensive. A cluster of tense pea-sized bullae was present in each axilla (Fig. 1): crusted erosions up to an inch in diameter were scattered over the chest and shoulders, and large intact bullae up to $\frac{1}{2}$ inch in diameter were grouped in the groins and suprapubic area. Many dusky erosions of ruptured bullae were present in the same area. On the upper part of the right thigh was a single red slightly raised disc 4 inches in diameter with erosions at the centre and bullae at the edges (Fig. 2).

Histology.—There is a sub-epidermal bulla. It is situated in the upper dermis, and is roofed by the intact epidermis. There is no acantholysis. The bulla has rounded margins, and contains considerable numbers of eosinophil leucocytes with a few neutrophil leucocytes and histiocytes.

There is a light infiltration of eosinophil and neutrophil polymorphs in the adjacent dermis, which also shows considerable oedema.

Treatment was commenced with corticotropin 40 mg. daily. In a few days all the cutaneous bullae had healed and in two weeks all the erosions had healed, but the thigh lesion left a red scar which has persisted. The mouth had improved, but vulval and anal erosions had not changed. Corticotropin increased to a dose of 50 mg.

daily had little effect on the mucosal lesions. Delta-cortisone was substituted in a dose of 30 mg. daily. Two days later there was a sudden relapse with pyrexia (101° F.) increase in buccal lesions and the reappearance of bullae on the scar on the thigh.

Increase in the dose of delta-cortisone to 40 mg. daily controlled the lesions and in a few days there was sufficient intact mucosa in the mouth for a few vesicles to form. Increase in the dose of delta-cortisone to 50 mg. and subsequently 80 mg. daily for a few days failed to prevent vesicles appearing in the mouth, but the erosions of the mouth healed steadily and the anal and vulval erosions healed completely.

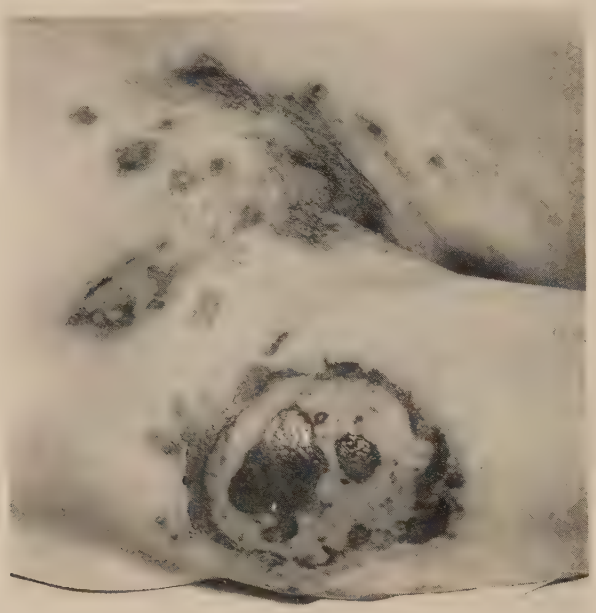

FIG. 2.

After three weeks' treatment with delta-cortisone the patient was discharged from hospital taking a dose of 40 mg. daily with all mucosal lesions healed except that mouth erosions were still present but have continued to improve. The conjunctivitis has subsided and although the adhesions are unaltered, the eyes are more comfortable than they have been for several years. The circinate scar on the right thigh still remains red.

No side effects were observed even on the highest dose of delta-cortisone, and weight and blood pressure have remained constant.

DISCUSSION.

The skin lesions in this case were more extensive than those usually seen in ocular pemphigus, though similar generalized bullous eruptions have been described by Rycroft (1934) and by Lever (1944) and in the earliest reference in the English language—Cooper (1858). As might be expected, the two occasions

in eight years when a skin eruption occurred coincided with a particularly severe exacerbation of the mucosal and conjunctival lesions. The lesion on the right thigh showed the features pointed out by Lever (1942, 1944) of recurrent bullae appearing on a circumscribed area and leading to scarring. It was noticeable that during treatment with ACTH and during the change over to delta-cortisone when the dose was lowered, the first sign of relapse was fresh blister formation in this erythematous and scarred area. The histological studies confirm those of Lever (1951) that the blister in ocular pemphigus is subepidermal in position and unaccompanied by acantholysis. Histological examination is therefore a valuable diagnostic aid in distinguishing the generalized eruption from that of pemphigus vulgaris.

Treatment.

Although hydrocortisone eye ointment appeared to benefit the conjunctival lesions during 1954 it was powerless to prevent the major relapses which occurred in February and August, 1955. The first bullous skin eruption in 1947 subsided without specific treatment, but the recent outbreak was so severe and her general condition was deteriorating so fast that treatment with corticotropin was started. The skin lesions were controlled within two weeks and the mucosal lesions improved considerably. However, she continued to produce fresh bullae in the mouth. It was considered that if the dose could be raised higher even the oral lesions might heal. Treatment was therefore changed to delta-cortisone and the dose raised to 80 mg. daily for a few days. Even on this dosage fresh vesicles appeared in the mouth; attempts to control the oral lesions completely were abandoned and she was discharged from hospital on a maintenance dose of 40 mg. delta-cortisone daily. On this dosage her skin remained healed and her eyes were more comfortable than they had been since the onset.

Summary.

A case of ocular pemphigus which has on two occasions in eight years developed a widespread bullous eruption is reported. Histological examination of the skin showed a subepidermal blister with no acantholysis, thus supporting the view that ocular pemphigus is a separate entity from pemphigus vulgaris.

The patient responded favourably to treatment with corticotropin and delta-cortisone, but it was not found possible to control all the mucosal lesions.

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PEMPHIGOID.
REPORT OF A ZOSTERIFORM TYPE.

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From the Departments of Dermatology and Internal Medicine of the Harlem Hospital, New York.

The term "bullous pemphigoid" was coined by Lever (1953) to designate a bullous eruption which developed chiefly in aged individuals with serious pre-existing disease. Interest has been centred recently in pemphigoid because of the high mortality rate in these patients even though the cutaneous disease is not considered to be directly responsible for the fatal outcome (Rook and Waddington, 1953). Apparently, the prognosis depends on the type of disease which existed prior to the onset of the cutaneous eruption. Pemphigoid has been observed in association with malignancy (Rook and Waddington, 1953), hepatitis (Epstein and Macaulay, 1948), chronic ulcerative colitis (Obermayer and Hartwell, 1954) and focal infections (Epstein and Macaulay, 1948). In a series of 38 cases reported by Rook and Waddington (1953) 31·5% of the patients died within $14\frac{1}{2}$ months after the bullous lesions were first noted.

Since no reference to a zosteriform type could be found in the literature, it was deemed worth while to document the following case.

Case Report.

A Negro woman aged 64 was admitted to hospital in coma. Her temperature was 102·6° F., the skin was dry and ichthyotic, and a diffuse hyperpigmentation was noted over the face and dorsal aspect of the hands. The sclerae were icteric. The liver, spleen and superficial lymph nodes were not palpable. The blood pressure was 200/90. Blood nitrogen and sugar determinations were normal; CSF normal.

Urine: straw coloured; bile and urobilinogen positive in dilution of 1–60; fluoresced yellow under filtered ultra-violet rays and qualitative analysis failed to show the presence of uroporphyrin.

Two days after admission consciousness was restored without palsies and the temperature dropped to 99° F. The patient gave a history of chronic alcoholism and of hypertension and for several years she had complained of weakness, anorexia, headache and dizziness.

The blood Mazzini test was negative, serum albumin was 2·8 g. and globulin 4·0 g.%, the cephalin flocculation test was 4 plus, the van den Bergh was positive direct immediate, icterus index 13 and the alkaline phosphatase 7·8 Bodansky units. Blood count: Hb 67%, RBC 3,150,000; lymphocytes 52%. An electrocardiogram showed possible myocardial damage.

About three weeks after admission a large tense itching blister developed on the dorsum of the left foot. About one month later a moderately itchy bullous eruption appeared on the left side of the chest, on both lower extremities, the right breast,

scalp and left buccal mucosa. Single lesions were noted in the latter three localities : relatively few bullae with grouping tendencies developed on the lower extremities but the eruption on the left side of the chest was massive and zosteriform in type (Fig. 1). It consisted of tense clear large bullae which originated from normal skin and on rupture their exposed pinkish red bases were hyperaesthetic and tender. These numerous, closely aggregated, discrete lesions extended from the vertebral column downward on the chest wall along the left 8th and 9th intercostal spaces, spreading sparsely over the upper abdominal wall and terminating at the umbilicus. The lesions tended to heal slowly and recurrences were common.

A favourable response was obtained with oral cortisone therapy and on discharge 3½ months after admission a few active lesions remained. At this time the van den Bergh and icterus index tests were normal, but the cephalin flocculation test was still 4 plus and the alkaline phosphatase had increased to 10 units.

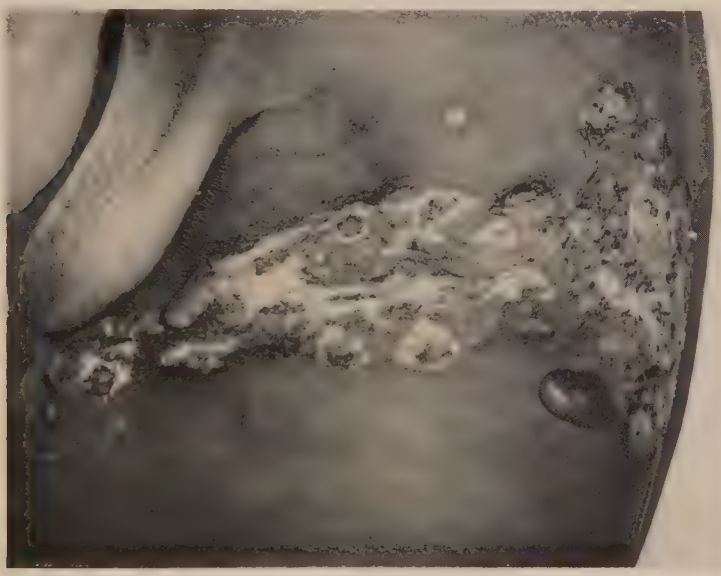

Fig. 1.

Histology. The inflammation was noted largely in the upper fourth of the cutis. A subepidermal bulla, containing fibrin in which were enmeshed many eosinophils, some polymorphonuclear leucocytes and a few lymphocytes, was a striking feature. Balloon cells were absent, and there was no evidence of acantholysis. A small segment of the peripheral portion of the bulla was intra-epidermal : here its base consisted not only of basal cells but also of several layers of prickle cells. The epidermis adjacent to the bulla was irregularly acanthotic and a cleft separated it from the cutis. Here the basal cells and the lowermost prickle cells showed both intercellular and intracellular oedema.

Below the bulla the papillae and subpapillae were oedematous, and within these areas the blood vessels were dilated and surrounded by sparse numbers of lymphocytes and an occasional eosinophil and polymorphonuclear leucocyte. A few blood vessels in the mid-cutis were mildly dilated, but the surrounding infiltrate was extremely sparse. The subcutis was normal.

Discussion.

Pemphigoid has been called both bullous dermatitis herpetiformis (Epstein and Macaulay, 1948) and senile dermatitis herpetiformis (Rook and Waddington, 1953). This cutaneous syndrome, which manifests itself in the aged, appears to be a distinct clinical entity. Lever (1953) has included under the title bullous pemphigoid a similar disease occurring in children of pre-school age, but this is open to question in view of its benign character in early life.

Although differentiation of pemphigoid from dermatitis herpetiformis may be difficult, the present case could not be classified under the latter disease because of the presence of the initial bullous lesion on the foot which appeared one month prior to generalization, the asymmetrical distribution of lesions and the involvement of the buccal mucosa. The zosteriform arrangement of the bullous eruption on the left side of the chest was unique and suggested the possibility of posterior root ganglion involvement.

The present patient had hypertension complicated by a cerebrovascular accident and, in addition, alcoholic cirrhosis of the liver. That the cutaneous manifestations developed on the basis of hepatic insufficiency is a definite possibility. Porphyria was ruled out by the absence of urinary porphyrins ; pemphigus vulgaris and herpes zoster generalisata were excluded by histological study.

Summary.

The case is reported of pemphigoid in a Negro woman aged 64. She had hypertension with a cerebrovascular accident and alcoholic cirrhosis of the liver.

The cutaneous lesion may have developed on the basis of chronic hepatic insufficiency. Its zosteriform arrangement was unique and suggested the possibility of posterior root ganglion involvement.

I am indebted to Mr. Edward Entin for the photograph.

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ROYAL SOCIETY OF MEDICINE

SECTION OF DERMATOLOGY

President—Dr. Reginald T. Brain.

19 May 1955.

Kaposi's Sarcoma.—Dr. R. G. Howell (for Dr. G. B. Mitchell-Heggs).

Mr. M. D—. Aged 72. Retired.

History of present illness.—For about 15 years he has had symptomless smooth red-brown plaques on the feet and legs.

In September 1954 he developed a widespread red scaly itching rash which began with circumscribed infiltrated plaques on the wrists and forearms, and gradually spread over much of the body including the face and neck. This rash began to subside in December 1954 while in hospital for investigation, when he was treated with antipruritics and sedatives only. Further improvement occurred when he received Plexan 1 c.c. i.m. twice weekly in February and March 1955. There are now only a few superficial scaly patches on the legs and trunk.

There has been no change in the original infiltrated red-brown plaques.

Previous history.—Mild Parkinson's disease for 10 years. Eczema of arms 5 years ago.

On examination.—Examination in hospital in December 1954 showed an anxious old man with a mild parkinsonian tremor.

There was a widespread red scaly, itching rash.

There were brown-red, well demarcated smooth infiltrated plaques on the feet and ankles, below the right knee and on the right buttock.

Some lesions on the ankles were atrophic and those on the right knee and buttock were considerably infiltrated.

B.P. 170/100: Soft apical systolic murmur. No oedema of ankles. Liver edge palpable. Spleen not palpable. One palpable lymph gland in right supra-clavicular fossa.

Investigations.—Hb. 85%. WBC. 9000: neutrophils, 52%: eosinophils, 1%: lymphocytes, 44%; monocytes, 3%. The WBC has not varied appreciably.

W.R.: Negative.

Urine: No abnormality.

Chest skiagram: No abnormality.

ESR: 12 mm./1 hr. (Westergren).

Histology:

(1) *The infiltrated plaques on the right knee and right buttock.* The epidermis shows hyperkeratosis and some acanthosis. There is a diffuse infiltrate of lymphocytes and plasma cells in the corium. There is an increase of thin-walled vascular elements and blood pigment and extravascular red cells are present.

(2) *The plaque on the right ankle* shows atrophic changes only.

(3) *The lymph gland* shows sinus hyperplasia.

(4) *The red scaly rash from the left forearm in November* 1954. The epidermis does not show any diagnostic features. The mid corium shows wide arborescent spaces

lined with one layer of flat endothelial cells, and in several places there are papilloma-like growths intruding into the lumina. They are heavily infiltrated with round cells and a few plasma cells, some of which have changed into Russell bodies. There is also a diffuse infiltration of round cells between the vascular spaces, and spindle cells and extravasated red cells are present.

(5) *The red scaly rash in March* 1955 shows eczematous changes only.

Summary.—" This is a case of Kaposi's sarcoma, which also shows in some places an increase of lympho-reticular tissue. It may be only a reaction to the vascular tumour formation or a concomitant reticulosis."—Henry Haber.

Comment.—The interest of this patient with Kaposi's sarcoma is that he had an episode of widespread erythrodermia, the histology of which suggested a co-existing reticulosis.

I am indebted to Dr. Haber for his interpretation of the histology.

Reference.

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? **Sarcoidosis.**—Dr. Patrick Hall-Smith.

Mrs. E. M—, aged 61.

History.—Twelve years ago first lesion appeared on neck; since then gradual development of similar areas, involving scalp, forehead, neck, shoulders and arms. The small lesion on her right arm has developed in the past six months.

Attended Middlesex Hospital on one occasion in 1948: a biopsy at that time suggested sarcoidosis rather than lupus vulgaris. X-ray of chest, feet and hands were normal, and a Mantoux 1 : 1,000 led to blistering.

Past history.—Glands right side of neck as a child. Nil else relevant.

Family history.—Sister with "lupus" of ear—diagnosed and treated before war (details not available).

On examination.—Multiple, round and elliptical, brownish, semi-translucent areas $\frac{1}{2}$ to 2 in. diameter involving scalp, forehead, neck, shoulders and arms. Apple jelly nodules on diascopy.

Small hard glands palpable in posterior triangles of both sides of neck.

Other systems normal.

Investigations.—Mantoux 1:1,000 blister reaction, 1:100,000 positive. W.R. negative.

Histology (Dr. J. McMurray).—Microscopically the appearance is that of sarcoidosis.

Skiagrams 19 *April* 55.

Chest: There are calcified hilar paratracheal and cervical glands. The lung fields are clear.

Hands: There is one slight cystic-looking area in the terminal phalanx of the left 4th finger. Osteoarthritic changes are present in the interphalangeal joints.

Feet: No bony abnormality.

Treatment.—In the past has received vitamins, P.A.S. and gold injections from her own practitioner.

26 April 55; Course of ACTH by drip over 5 days.

7 May 55: Local infiltration of lesions left upper arm with hydrocortisone acetate; injections ranging from 10 mg. to 25 mg., depending on size of lesion. There has been little perceptible change as yet.

Comment.—The interest of this case is that clinically and histologically it is very difficult to determine whether we are dealing with a case of sarcoidosis or lupus vulgaris. Histological opinion leans towards a diagnosis of the former and a positive

Mantoux reaction is no bar to a diagnosis of sarcoidosis. Regression of the lesions following local injection of hydrocortisone acetate might have been expected in sarcoidosis, but so far this has not occurred.

It is intended later to watch the effect of treatment with isonicotinic acid hydrazide.

The PRESIDENT: I should have thought that the clinical picture conformed to our concept of lupus vulgaris and I should be very reluctant to use ACTH. Undoubtedly the features were confusing in the scalp at first.

Dr. P. BORRIE: I do not think anyone need be too frightened of using cortisone in lupus because it is used in sanatoria for pulmonary tuberculosis not only for suppressing drug reactions but in its own right.

Dr. L. FORMAN: The diagnosis of sarcoidosis should be considered, for some of the areas have been present for 10 years and there is no scarring.

Dr. N. A. THORNE: At the meeting of this Section on 17 April 1952 I showed an extensive case of lupus vulgaris involving the greater part of the face and neck. Although untreated for over thirty years, no scarring was present.

I have also seen another extensive and untreated case of some ten years' duration without sign of scarring.

Having seen a large number of cases of lupus vulgaris in the Lupus Clinic at the London Hospital, I feel that this is the type of case where one should make the diagnosis on clinical signs rather than on the histological appearance.

Lentigo Maligna of Cheek and Pre-cancerous Melanosis of Conjunctiva.—Dr. I. A. MAGNUS (for Dr. E. J. MOYNAHAN).

Mrs. A. P—, aged 75.

The patient when first seen two weeks ago stated that she thought that the lesion on the left cheek had been present for about twenty years and that it had slowly

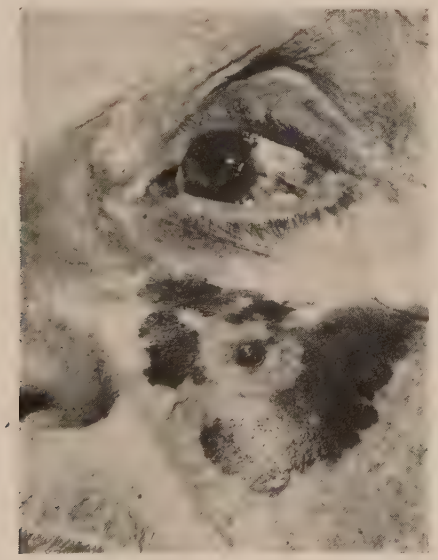

FIG. 1.

spread. There is now a flat, irregular ring of brown pigmentation enclosing a relatively unaffected area in the centre of which is a blue-black, nipple-like nodule, which was said to have appeared two months ago and to have arisen on normal skin. (Fig. 1).

Although the patient was not aware of it the left eye was also affected. Areas of brown pigmentation affect the bulbar conjunctiva, the limbus and parts of the adjacent cornea. She was seen by Mr. Cook in the Eye Department. With the slit-lamp microscope particulate pigmentation could be seen extending into the episclera.

The lesion on the cheek seems to be an example of a malignant melanoma arising from what Hutchinson first described as the melanotic or infective freckle. In the literature the commonest site for lentigo maligna, after the cheek, is the eyelid or conjunctiva. The appearances under the slit-lamp microscope of the conjunctival lesion in this patient are such that the condition must be regarded as pre-cancerous, a diagnostic feature being extension of the pigmentation from the bulbar conjunctiva into the limbus and cornea and down into the episclera.

Dr. Moynahan: I think that we shall find in the centre of that elevated lesion a melanotic carcinoma as happens in many of these cases. As they are relatively benign we propose to do a local excision and if necessary later, if the conjunctiva indicates a melanotic change, to enucleate the eye. I gather there have been cases of melanotic freckle that have had a relatively good prognosis even though it may indicate a carcinomatous change.

Thibierge—Weissenbach Syndrome (Scleroderma with Calcinosis).—Dr. J. C. Frith (for Dr. R. J. Harrison and Dr. M. Feiwel).

Mrs. K. R—, aged 60, was shown to this Section on 19 May 1955. It was thought that a report of biochemical investigations made from June 1954 to June 1955, correlated with the clinical picture would be interesting.

Clinically, at the beginning of the period the hands showed deformities but no obvious calcium deposits: radiologically, however, deposits were very obvious. At the end of this time there were subcutaneous deposits in the fingers, and radiologically, the masses of calcium had increased.

Past history.—In 1946 she started to get "pins and needles" in the left hand and seven months later in the right hand. The fingers gradually became deformed, and were also very cold in the winter. In 1953 she began to have "horrible feelings" in the tips of the fingers, the picture suggesting one of Raynaud's phenomenon. Since 1948 she had had pains in the elbows, shoulders and knees, and in 1953 she developed congestion of the lungs and had been followed up in the chest clinic because of persistent shadowing at the bases.

History.—The patient first attended hospital on 20 April 1954, because of an intractable ulcer on the left leg. A boil had appeared over the head of the left fibula five weeks previously, and had not healed despite incision and penicillin.

Personal history.—She had lost one stone in weight during the last few years, and for the past six months she had had some difficulty in swallowing large pieces of food. Menopause in 1945.

Examination.—On admission, thin with visible veins on trunk. Deep ulcer $1\frac{1}{2}$ in. in diameter over the head of the left fibula. Hands: skin tight and shiny over the phalanges with some thickening, though sweat still being formed. The terminal phalanges, particularly of the first and second fingers on both hands, short. Some limitation in movements of joints of wrist, elbows, shoulders and knees. Minimal involvement of the face and lips, but mouth small when opened to its fullest extent.

Routine investigations:

Blood count: Hb, 78%; WBC 10,100; polymorphs 79%, eosinophils 2% lymphocytes 14%, monocytes 5%.

ESR.: Varied between 10–31 mm. in 1 hr. (Wintrobe).

Blood W.R. and Kahn: Negative.

Fasting blood sugar = 97 mg. per 100 ml.

Blood urea = 37 mg. per 100 ml.
Plasma uric acid = 4·1 mg. per 100 ml.
No L. E. cells seen in the peripheral blood.
Serum A.S.O. units per c.c. = 160.
Serum agglutinations were negative to: *Salmonella typhi* and *paratyphi*, non-specific salmonella *Br. abortus* and *melitensis*.
Urine: Acid with trace of protein. Leucocytes and epithelial cells present. Culture—light growth of *B. coli*.
Skin histology: Lichenification with changes in the collagen fibres suggesting scleroderma.
Oesophagoscopy: Nil gross abnormal.
E.E.G. normal. E.C.G. normal. B.M.R. + 34.
Radio-active iodine urinary secretion test: Normal.

Skiagrams:

Chest: Increased striation at both bases, right more than left.
Hands: Loss of phalangeal tufts of several terminal phalanges and in their place have been deposited granular masses of calcium. Further masses are visible around the wrist, thumb, elbow and shoulder joints.
Vascular: Arterial calcification in aorta and arteries of pelvis is also present.
Barium swallow: Lack of tonicity and elasticity in lower half of oesophagus.
I.V.P.: Normal.
Left knee: Osteoarthritic changes present.
Progress.—She was discharged on 2 July 1954 and followed up in Out-Patients. Subsequently the hands gradually became more painful and subcutaneous deposits of calcium appeared over the second phalanx of the left first finger, and also on the medial side of the distal interphalangeal joint of the left second finger.
No specific treatment was instituted.
Calcium metabolism in scleroderma.—The frequent association of diffuse scleroderma with calcinosis, usually referred to as the Thibierge-Weissenbach syndrome, has led to many studies of calcium metabolism in scleroderma.
Most authors have found normal serum calcium, phosphorus, and phosphatase levels.
Positive calcium balances have been reported by Paggi (1934), Cornbleet and Struck (1937), Byron and Michalover (1943); while normal ones were obtained by Rothman and Walker (1949) and Brooks (1934). The last author made interesting parallel studies on the calcium and phosphorus metabolism in a case of scleroderma, and a case of calcinosis universalis.
The development of the intravenous calcium tolerance test by John Eager Howard and his group (1953) makes it possible to study the dynamics of calcium metabolism in a number of disorders.
The current pattern of the test was evolved gradually as more experience was acquired. A dose of calcium salt (15 mg. calcium kg. body weight) was given in an intravenous infusion over a four-hour period. Blood and urine estimations of calcium and phosphorus were made before, during and after the infusion. They found that in normal persons tested the results ran in strikingly parallel fashion.
Russell Fraser and Nordin (1954) made observations on the effect of intravenous calcium gluconate and expressed phosphate excretion both in mg. per hour and as a phosphate-creatinine clearance ratio. The latter value is an index of the proportion of phosphate filtered by the glomerulus but not reabsorbed by the renal tubules, and thus indicates any specific changes in the renal handling of phosphate.
In June 1954 an intravenous test over a four-hour period (15 mg. calcium kg. body weight) was made on our patient. Nearly a year later, as her deposits of calcium had increased considerably, a second calcium tolerance test was done.

The phosphate-creatinine clearance ratio may be calculated from the following formula :

$$\frac{\frac{Up\ V}{P_p}}{\frac{Ucr\ V}{Pcr}} = \frac{Up \times Pcr}{Ucr \times P_p}$$

Up = Urinary phosphate concentration.
Ucr = „ creatinine.
V = „ volume per unit time.
P_p = Plasma phosphate concentration.
Pcr = „ creatinine.

Methods.—Phosphorus was estimated by the method of King (1951) and also by a modification of the method of Fiske and Subbarrow ; calcium by the method of Clark and Collip ; plasma and urine creatinine by the alkaline picrate method of Roscoe (1953).

Results :

	1954.	1955.	Normal values.
Serum calcium (mgm. %)	10·5	10·6	9 –11
Serum phosphate (mgm. %)	3·5	3·8	2·5 – 4·5
Serum creatinine (mgm. %)	1·0	1·0	0·1 - 2·6
Total			
Protein (gm.)	7·7	7·6	6·3 – 8.2
Albumin	3·7	3·6	4 0 – 5·7
Globulin	4·0	4·0	1·5 – 3.0
Alkaline phosphatase (K.A. units)	5·6	5·4	3·3 –12·9
Phosphate-creatinine ratio	0·14	0·18	0·08–0·18

The calcium tolerance test on both occasions gave a normal phosphate-creatinine clearance ratio, i.e. the renal clearance of phosphate was within normal limits. Similarly the renal excretion of calcium was, on both occasions, within the normal range.

In so far as can be measured, therefore, this patient had no inherent defect in the metabolism of calcium or phosphorus after her equilibrium had been overloaded by an excess dose of calcium intravenously.

Summary.—A case of Thibierge-Weissenbach syndrome was shown in which the degree of calcinosis progressed considerably over a period of a year.

Calcium tolerance tests after an interval of nearly a year showed no inherent defect in metabolism of calcium and phosphorus.

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Scleroedema.—Dr. D. I. Williams.

D. C—, aged 35 years. Occupation : Road sweeper.

History.—In May 1954 he attended the Ear, Nose and Throat Department with pain in the left ear and swelling on the left side of the neck present for the previous ten days. Five days before this he had noticed swellings on both temples following the second injection of penicillin given for a dog-bite on the right leg. Apart from slight reddening of the floor of the external auditory meatus and an ill-defined swelling below the left ear no abnormality was found at this time. During the ensuing months he developed further transitory swellings on the temples, sides of the neck, eyes and lips and he found it difficult to put on his collar owing to the swelling of the neck. In the past few months he has become increasingly short of breath on exertion and has complained of left-sided low back pain on walking. His abdomen has felt tight and distended. He denied having any skin rashes or muscular weakness, and no definite history of preceding upper respiratory infection was obtained.

Past history.—Pleurisy 8 years ago. Slight bronchitis since childhood.

Family history.—Nil relevant.

On examination.—The skin of the whole body, except over the hands and feet and to a lesser extent the supraclavicular region, is pale, tense, indurated and "oedematous." There is no pitting oedema except to a slight extent on the lower limbs. Firm swellings are present over both temples and the oedema of the face, which involves the lips and the eyelids, has obliterated the normal skin creases. The skin cannot be pinched up and is firmly adherent to the underlying subcutaneous tissue. Over the the beard area and trunk a number of hairs are being extruded from their follicles. Movement of the limbs and chest is restricted by the oedema, but no definite muscle weakness is present. Examination of other systems reveals no abnormality.

Investigations :

(1) Blood count : Haemoglobin 102%, white cell count 6700 cmm. Film appearances normal.

(2) ESR : 6 mm./hour.

(3) Urine : Occasional pus cells and hyaline casts. No granular casts.

(4) Blood urea : 39 mg.

(5) Plasma proteins : 6·8 g. 100 ml. Albumen 4·68 g./100 ml. Globulin 2·12 g./100 ml.

(6) Electromyogram : Normal.

(7) E.C.G. : T waves flat in VF V5 and V6

(8) Skiagram of chest : Normal.

(9) Barium meal : Oesophagus, stomach and small intestine appear normal.

(10) Histology (Right arm) : No abnormality could be detected in the skin or underlying muscle.

Treatment.

(1) Nivaquin 200 mg. *b.d.* since 10.v.55.

(2) Hyalase 1000 units in 1 c.c. injected subcutaneously on three occasions into the same area.

(3) Hydrocortisone acetate 25 mg. in 1 c.c. subcutaneously on one occasion.

Up to the present time his condition has not improved.

Case for Diagnosis. ? Lupus erythematosus, ? Lichen planus, ? Erythema figuratum perstans.— Dr. Theresa Kindler.

Mrs. M. A—, aged 71, housewife.

She was first seen in 1948 and reported that the rash had been continually present for a year and had started behind the right ear with a few scaling spots. There were

two patches of grouped lesions, one the size of a man's palm extending from the right neck to the shoulder, the other florin-sized behind the right ear. They consisted of coalescing, scaling dull-red slightly infiltrated papules, forming a serpiginous outline. The centre was depigmented and showed a few scattered discrete lesions. The clinical picture at that time suggested a tertiary syphilide or possibly lupus. In the course of observation the rash assumed various other patterns, such as rings or half-rings, and through their coalescence, gyrate or festooned forms. They had a broad, flat, red, scaling inner margin and a very narrow, slightly raised, dark-red outer edge (Fig. 1). There was peripheral extension and clearing in the centre. The

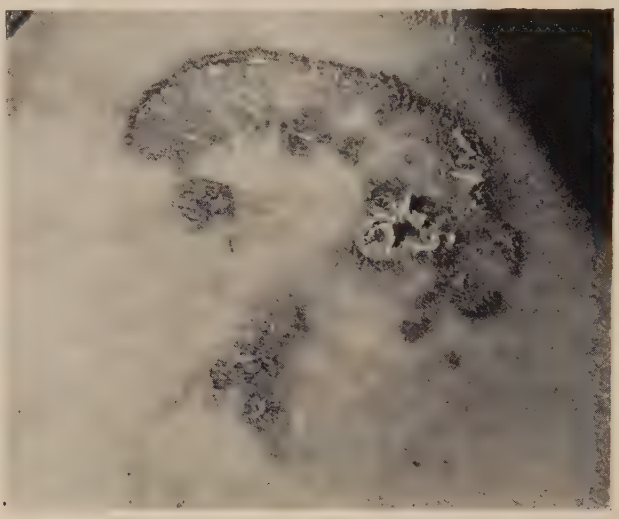

Fig. 1.

development was very slow, but after many months the lesion invariably resolved spontaneously, leaving a hardly visible, slightly depigmented patch. Usually several plaques in various stages of development were present simultaneously. The skin was never free of lesions. The non-exposed areas about the nape of the neck, shoulders, upper chest and behind the ears have been exclusively affected. As a rule the lesions were symptomless, but there was sometimes, independent of the season, an exacerbation with slight weeping and soreness.

Past history.—She had eczema as a child and had a rash on her hands and behind her ears at the age of 30. She has taken no drugs.

Other illnesses.—She suffers from osteo-arthritis, chronic bronchitis and bronchiectasis.

Present condition.—At the base of the right side of the neck, extending over the lateral part of the clavicle is an arc-shaped lesion, 3 in. in diameter, similar to that described above and illustrated in Fig. 1. There are several discrete and confluent satellite lesions in the adjoining areas of neck and shoulder. The face, the rest of the body and the mucous membranes are free. There is some gingivitis. The vermilion part of the lips is greyish-opaque, but shows no scarring.

Investigations.—W. R., Kahn repeatedly negative. Blood count normal. E.S.R. (Westergren) 17 mm./hour.

Plasma proteins, 7·79 g. % ; albumin, 5·0 g. % ; globulin, 2·79 g. %.

Skiagrams.—Nose : no abnormalities detected ; hands, osteo-arthritis in all interphalangeal joints. Tomogram of chest suggests bronchiectasis.

Scraping and culture for fungus negative.

Histology.—Lesion on right neck (1948) : Epidermis in parts atrophic. Very little general keratosis and some keratotic plugging. There is liquefaction degeneration of the basal layer.

The upper cutis is oedematous, the capillaries are dilated. The infiltrate is generally scanty and shows peri-vascular and peri-follicular arrangement. It consists mainly of lymphocytes, a few plasma cells and fibroblasts. Some of the follicles are much dilated and filled with concentric masses of keratin. In the subepithelial layer the elastic fibres are scanty and the collagen does not stain well.

Section from base of neck (1952) : Within the lesion at the left half of the section there is hyperkeratosis and acanthosis with irregular lengthening of the rete pegs. The granular layer is increased, the basal layer shows hydropic degeneration and disarrangement of cells. There is a dense, band-like, predominantly lymphocytic infiltrate sharply limited to the upper part of the cutis. There is invasion of the lower epidermis by the infiltrate cells.

At the right side of the lesion the infiltrate stops fairly abruptly. There is here a scanty focal infiltration around the capillaries and follicles. Here the horny and granular layers are thin. The cutis is oedematous ; the elastic fibres have almost disappeared and the collagen fibres show basophilic degeneration in the upper cutis.

Treatment.—The patient received short courses of bismuth injections, mepacrin and pot. iodide and various local applications, including hydrocortisone ointment, but there was no response.

Discussion.—The histological pictures of this case varied considerably in two biopsies taken at different times. While the section taken in 1948 perhaps suggested lupus erythematosus, another one in 1952 simulated lichen planus. The clinical features do not conform to either disease. The exclusive involvement of covered or at least non-exposed areas, the slow but unfailing spontaneous resolution without scarring, the migratory character of the condition over a limited area, the lack of response to recognized treatments, and the second biopsy are not in keeping with the diagnosis L.E., in spite of a certain similarity of the lesions to L.E. in some stages. Against the diagnosis of lichen planus there is the appearance of the first biopsy, the extraordinary chronicity and continuous recurrence of the lesions, the frequent changes in their appearance, the comparative absence of subjective disturbance except for occasional soreness, and the absence of lesions of the mucous membranes.

The clinical course and appearance, I think, has many features in common with that group of erythemas to which attention was first drawn by Colcott Fox (1881) who named them erythema gyratum perstans, and of which the erythema annulare centrifugum of Darier is a variety. The lesions of the present case, however, do not show the cord-like margin and absence of scaling of Darier's disease, and resemble more the cases which Wende described (1908). He summed up their characteristics as follows : " The disease begins with scattered, isolated papules which tend to fade at the centre while extending peripherally, thus forming circinate, erythematous outlines. The outer half of the advancing margin is smooth and slightly raised, the inner edge desquamating. The larger lesions vary in size from a 25-cent piece to the palm of the hand. The rings assume circinate, annular, discrete, confluent gyrate or zig-zag forms. Subjective symptoms may or may not be felt."

A similar case in a brother and sister was reported by Adamson (1906).

Graham and Throne (1930), whose description was similar to Wende's, stress the fact that the surface over which the disease has travelled frequently looks normal.

The appearance of and changes in the histological pictures is puzzling. The histopathology has usually been reported as that of a non-specific inflammation. Although

it may have been modified in the present case by senile changes, this does not account for the acanthosis, band-like infiltrate, the invasion by infiltrate of the lower epidermis and the changes in the basal layer.

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Dr. Arthur Jarrett : I suggest that it is lichen planus erythematosus ; clinically it resembles lupus erythematosus and histologically it is lichen planus. I have seen a similar case with extensive lesions on the face and forearms which was thought to be lupus erythematosus, possibly a sub-acute type as she had had some undiagnosed abdominal pain. The histology of the lupus erythematosus-like lesions was that of lichen planus. Later she developed frank lichen planus papules on the forearms and these were found to have the typical histology of this condition.

Dr. Borrie : We have had cases such as this in which it is apparently impossible to decide on a diagnosis. One day it looks like lichen planus, the next like lupus erythematosus. I suggest that we keep an open mind rather than decide whether we will accept the histological or clinical findings. I think clinically lupus erythematosus is suggested and histologically it is lichen planus.

The following cases have been published in *Proc. R. Soc. Med.*, **48**, 774.

Idiopathic Steatorrhoea.—Dr. P. D. Samman.
Facial Hemiatrophy.—Dr. Peter Borrie.
Case for Diagnosis.—Dr. E. N. Johnston for Dr. H. J. Wallace.
The following cases also were shown :
Alopecia Areata.—Dr. L. Forman.
Pityriasis Lichenoides et Varioliformis.—Dr. P. D. Samman.
Monilethrix Regrowth After Treatment with ACTH.—Dr. E. J. Moynahan.
Erythrasma.—Dr. C. M. Ridley for Dr. J. S. Pegum.

OBITUARY.

Dr. H. W. WILSON.

Harold William Wilson died at his home in Auckland at the age of 69.

He was born in New Zealand, was educated at Warganni Collegeate School and commenced his medical education at Edinburgh University in 1908. He graduated in 1913 and at the outbreak of the Great War volunteered in the R.A.M.C. and served in France, Belgium and Egypt with the rank of Captain. At the end of the war he returned to New Zealand for 2 years and in 1920 went back to Great Britain for his dermatological training. He was attached to the Manchester and Salford Skin Hospital and later to the Skin Department of the Royal Infirmary, Edinburgh. He became M.D., Edinburgh, in 1923 and was awarded the Gold Medal.

After further study in London and in Europe he returned to Auckland in 1924 and commenced practice as a dermatologist. He joined the honorary staff of the Auckland Hospital in 1924 and set up the first skin department there, remaining in charge of that department until his retirement in 1952. At the time of his death he was dermatologist to the Mater Misericordia Hospital, Auckland, and was consulting dermatologist to the Auckland Hospital. He was a Foundation Fellow of the Royal Australasian College of Physicians, an original member of the Auckland Branch of the British Empire Cancer Campaign Society, a foundation member and past president of the New Zealand Dermatological Society, a foundation member and past president of the Auckland Clinical Society, honorary member of the Dermatological Association of Australia, and a past chairman of the Staff of the Auckland Hospital.

Dr. Wilson was not only a dermatologist of great skill, wide experience and unusual tenacity, but was a doctor of outstanding kindness and sympathy who was held in great affection by his patients. By his careful and interested teaching of generations of students and residents at Auckland Hospital he made a great contribution to medicine in New Zealand.

Outside his profession, he was an enthusiastic angler and a keen gardener, and was a warm-hearted and accomplished host to his many friends. He is survived by his wife, to whom we extend our sincere sympathy. R. F. T.

Dr. JOHN WITTON FLYNN.

John Witton Flynn has left us—at the comparatively early age of 60 from a coronary attack at his home on 6 December 1955—and Australia will be the poorer for his passing. He was a member of a well known Sydney medical family of high esteem. His father was a doctor and all six sons graduated in medicine. He loved life ; he loved his fellow men ; he loved his country and served her, faithfully and enthusiastically, both in peace and war. By any standards, he was a great Australian and a great dermatologist.

The writer first met John Flynn in 1916, abroad in the Great War, where they served together in France in the 30th Battalion, Australian Imperial Forces. In common with so many young men of that period, he had put studies aside and at the end of his third year in Arts, after graduating B.A., he enlisted. He soon gained a commission as a subaltern and became popular with his men and his fellow officers and he proved a gallant, good and indefatigable soldier. Shortly after the great break-through on Ludendorf's Black Day (8 August 1918) he was wounded severely, losing an eye, and it was during this action that he was awarded the Military Cross.

On returning to Australia he again took up his studies at Sydney University, despite the handicap of the loss of his eye, and he entered second year medicine. After graduation, he became a R.M.O. at the Sydney Hospital and on completion of his term of office, he left Australia to do postgraduate work in dermatology, to which he had been attracted as a student. Before leaving he was married to Miss Mary Bridge and she accompanied him abroad. He worked hard in London and elsewhere and soon became attached to Dr. W. J. O'Donovan of the London Hospital and Dr. A. C. Roxburgh of St. Bartholomew's Hospital, accompanying the latter on a dermatological " holiday " to Vienna.

On his return to Australia, he established himself in Macquarie Street as a dermatologist. Success was not long delayed : he was well trained, well known and popular.

He later became the Skin Consultant to the Royal Australian Navy and the Royal Australian Air Force, and during World War II spent some months travelling in the South Pacific, on dermatological consulting work for the R.A.A.F., in which he reached the rank of Group Captain. He was one of the oldest Australian members of the British Association of Dermatology and also a past president of the New South Wales branch and a past president of the Dermatological Association of Australia, of which he was a Foundation member. At the time of his death, he was the President of the New South Wales Medical Board, on which he had served as a member for years.

Never one to sit passively at any meeting, social or medical, his views given positively, sometimes trenchantly, were always listened to—if not always accepted—for he had a gift of cutting through non-essentials and getting down quickly to the core of the subject. He had a mordant humour and sometimes a biting sarcasm, but he never nursed a grudge. To those postgraduates, particularly the men doing the Diploma of Dermatological Medicine, who attended his popular Wednesday Clinics at the Lewisham Hospital, Sydney, he would reiterate that dermatology is still more an art than a science, and he would appeal for a common-sense approach to it. He insisted that treatment, worked out by experience over the years, both abroad and at home, should not be discarded for the newest things that the drug house representatives put forward ; at the same time he kept abreast of modern treatments. As a teacher, he was enthusiastic, lucid, refreshing and dogmatic.

As the years went by, he became a recognized figure in the racing world, a sport which he loved deeply throughout his life. He was a grand host at his beautiful home in Bellevue Hill, and it was indeed a pleasure to be entertained there by him and his charming wife and daughter, Susan.

Thus lived and died an outstanding personality in Australian Medicine : a man with many lovable traits. Farewell, John. You will be long remembered. F. C. F.

BOOK REVIEW.

Actinotherapy.*

This little book is well described as " a review of the literature, giving an outline of indications and technique ". It opens with a history of actinotherapy, followed by useful physical and physiological data.

The author is at his best in the chapter on technique and dosage. One wonders why courses of treatment are designated as " sedative ", " tonic ", or " therapeutic ", when in fact " sedative " means suberythema to first degree erythema exposures ; " tonic " means first degree erythema exposures ; and " therapeutic " means first to second degree erythema exposures followed by pigmentation. Perhaps the " therapeutic " course explains that mystery : what it is that patients are referring to when they speak of the " therapy treatment " they have been receiving.

The two chapters on the uses of ultra-violet rays in dermatology consist mostly of lengthy verbatim quotations from the writings of eminent dermatologists. It is useful to have these opinions collected together. Six pages are given to the treatment of pyodermas and impetigo ; the technique of treating ulcers, bed-sores, infected wounds and sinuses is also described. The reviewer does not agree with the curt dismissal of carbon arc lamps as follows: " Carbon arc lamps are still employed to some extent in medical treatment, but taking all the various factors (strength of output, spectral quality, convenience, cleanliness) into consideration, the medium pressure mercury vapour discharge has been found the most satisfactory, and is most generally used " (page 21). Similarly, in discussing the treatment of lupus vulgaris, a few pages might have been spared to describe the use and undoubted advantages of the Finsen-Lomholt lamp over the Kromayer lamp ; but we read " The apparatus of choice for this purpose is the Finsen-Lomholt lamp, but since this is available only in a very few centres, the use of the Kromayer lamp only will be described " (page 80).

Presumably on page 31 the author means oxidation when he refers to " exudation of bleached pigment already in the skin from previous tanning " as being related to the rapid pigmentary reaction after exposure to the sun. Incidentally, can it really be true that the role of pigmentation in warding off sunburn is a minor one? If it is true that the thickness of the stratum corneum mainly offers that protection, it needs explaining why Scandinavians tend to be blondes and tropical Africans black, with all gradations between.

Chapters follow on the treatment of sundry rheumatic, allied and miscellaneous conditions, and finally there is a chapter on ultra-violet diagnosis.

Readable and well compiled, it is a pity that from page 1 onwards an attitude has been adopted of petulent protestation against actinotherapeutic doubters. This endogenous heat makes it more difficult for the reader to keep cool and objective when reading about, let us say, the thermal effects of radiation incident upon the human skin.

B. F. R.

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* *Modern Actinotherapy.* R. H. Beckett, B.A. London : William Heinemann. Pp. 161. 20 figs. and 5 plates in colour. Price 17*s.* 6*d.*

CURRENT LITERATURE

ON THE NATURE OF THE ECZEMATIC COMPONENT OF OXIDIZED Δ^3-CARENE. S. Hellerström, N. Thyresson, S. Blohm and G. Widmark. (1955) *J. invest. Derm.*, **24**, 217.

Freshly distilled turpentine gives less trouble than that which has been exposed to oxidation, and French turpentine, which contains no Δ^3-carene, much less than Swedish.

It has been possible to show a relation between absorption of oxygen, polymerization, and allergic potency; but thermolability has frustrated attempts to isolate the active fraction.

J. H. T. D.

A CLINICAL EVALUATION OF A PIPERIDINE COMPOUND ALONE AND COMBINED WITH CALCIUM INTRAVENOUSLY IN ANTIHISTAMINE THERAPY. F. C. Combes and M. Reisch. (1955) *J. invest. Derm.*, **24**, 191.

A therapeutic trial without controls in 135 private patients with unspecified dermatoses. "All patients, as far as could be determined, were apparently in good health except for their dermatoses." J. H. T. D.

SOME OBSERVATIONS ON THE NATURE, ORIGIN, AND POSSIBLE FUNCTION OF THE SQUALENE AND OTHER HYDROCARBONS OF HUMAN SEBUM. B. Boughton, I. S. Hodgson-Jones, R. M. B. MacKenna, V. R. Wheatley and A. Wormall. (1955) *J. invest. Derm.*, **24**, 179.

Squalene may have something to do with the metabolism of cholesterol. *In vitro* it is fungistatic and carcinogenic hydrocarbons are destructively oxidized by it. It inactivates free sulphydryl groups and inhibits succinic dehydrogenase. In rabbit and guinea-pig, though not in man, it is depilatory. It has no obvious effect on keratinization or pigment.

There is less of it in the skin of children than of adults, but no more in the bald than in the hirsute and very little more in males than in females. It is not a cure for psoriasis or eczema.

The quantities recovered vary in the individual from day to day; but it has not been possible to show that ingested squalene is excreted through the skin or that the secretion is influenced by menstruation. J. H. T. D.

TINEA CAPITIS. AN EPIDEMIOLOGICAL THERAPEUTIC AND LABORATORY INVESTIGATION OF 6,390 CASES. A. Dostrovsky, G. Kallner, F. Ranbitschek and F. Sagher. (1955) *J. invest. Derm.*, **24**, 195.

Comprises all cases treated in the department of dermatology of the Hadassah University Hospital between 1926 and 1953. X-ray epilation by means of a 5-source irradiation divided into five daily exposures, plus after-treatment with iodine, yielded 97·5% success. Thallium used for various reasons in 194 cases had a 47·6% relapse rate and was therefore soon abandoned. Of 1358 cultures 1038 were positive: 80% yielded *T. violaceum*, 12% *T. schonleini* and microsporons only 1·7%. No microsporons at all were cultivated during this period from immigrants.

J. H. T. D.

MUSCLE STUDIES IN CUTANEOUS DISEASE. P. A. O'Leary, E. H. Lambert and G. P. Sayre. (1955) *J. invest. Derm.*, **24**, 301.

The authors, in their anxiety to make it clear that the muscles underlying an area of skin showing the specific changes of dermatomyositis are not necessarily themselves involved, stress the desirability of making separate biopsies of muscle and skin. Surely the deeper incision required for muscle biopsy would have a prescriptive right to cleanly opposable edges? Excellent microphotographs show five types of muscle lesion.

Electromyography is said to have some place in the early diagnosis of skin lesions associated with symptoms of muscular weakness. J. H. T. D.

THE ALLERGY OF INFECTION. STATEMENTS, SPECULATIONS AND SYNTHESIS. M. Leider. (1955) *J. invest. Derm.*, **24**, 255.

This concise and ingenious oversimplification should at least help us all to get a clear picture. There are two kinds of microbial attack. In one the microbe secretes a primary irritant or toxin and against it we have to manufacture and take into stock a neutralizing antibody. Having recovered from such an infection or even merely having provided our defence mechanism with a sample of the toxin our tissues become to some extent immune and the toxic effect is diminished or abolished. This is, of course, a form of allergy, though not habitually so regarded.

But the idea of allergy is quite inseparable from the current theory of the other sort of infection, in which the microbes produce no primary irritant but in which the tissues, after an incubation period, may develop a most violent intolerance of it and its products. Allergic states of this type vary from one tissue to another and from one phase to another in the history of the illness.

For the sake of completeness it might perhaps have been well if the author had mentioned the reactionless presence of lepra bacilli in unsusceptible tissues and made it clear that the so-called "immune reaction" to cow-pox vaccine is not so much "like the chance immunity of syphilis" as a consequence of the soldier's prompt action in wiping it off with his cap.

In his specification of "ids" he says " . . . the *terminus* (why not 'termination' or 'suffix') is a good one to make comprehensible words to encompass all the lesions of diseases that have many expressions because of the many specific altered reactivities they develop." (But it would be churlish to submit to gratuitous odontoscopy this elegant and serviceable hippodorema which cannot fail to give the keenest pleasure to every serious student of medicine.)

J. H. T. D.

STUDIES OF PH OF SWEAT PRODUCED BY DIFFERENT FORMS OF STIMULATION. F. Hermann and L. Mandol. (1955) *J. invest. Derm.*, **24**, 225.

Sweat secreted under the local or parenteral influence of pilocarpine, acetylcholine, adrenalin, etc., is more alkaline (pH 7–8) than that provoked by exercise or by atmospheric heat (pH 4–5·5). The difference is not marked in women, whose sweat apparatus needs a lot more acetylcholine to make it function. In one case the same difference was observed in palmar sweat, indicating that the difference is not attributable to apocrine gland activity. Nor is there more CO_2 dissolved in exercise sweat. After very prolonged thermal sweating the pH value tends to rise, showing that the difference is not directly attributable to environmental temperature.

J. H. T. D.

SPECIAL FEATURES IN ALLERGY IN CHILDREN. Zaida Eriksson-Lihr. (1955) *Acta allergol.*, **8**, 289.

Of 4832 public school children in Western Finland 6·8% suffered from allergic diseases, the frequency of infantile eczema being 3%, and of urticaria 2·2%. Of 27,999 children in Helsinki 3·6% suffered from allergic diseases, the incidence of eczema being 2·1%. Both asthma and eczema were seen at an earlier age in boys than in girls. This was thought to be due to a relative hormonal insufficiency affecting particularly the pituitary cortical system. H. T. H. W.

MELANOMA OF THE NOSE AND EAR. M. Mason and I. Friedmann. (1955) *J. laryngol.*, **69**, 98.

The authors describe 21 cases, eight of which were "benign melanomata". All the cases of malignant melanoma died: 11 arose in the nose and 2 in the ear. The authors state that about half the cases of nasal melanoma are unpigmented and confirm the view that melanoma of the mucous membrane is almost always fatal. O. L. S. S.

THE PATHOLOGY OF MALIGNANT GRANULOMA OF THE NOSE. I. Friedmann. (1955) *J. laryngol.*, **69**, 331.

This is a review of 15 cases studied. The disease often starts with sinusitis, or even retro-orbital symptoms. The pathology and also the association with necrotizing vascular and granulomatous lesions of other organs are discussed.

This is an excellent review of lethal granulomatous ulceration of face and nose. O. L. S. S.

STUDIES IN ECZEMATOUS SENSITISATIONS: V. THE ROLE OF THE REGIONAL LYMPH NODE. Adolph Rostenberg, jnr. and William R. Best. (1955) *Arch. Derm. Syph., Chicago,* **72,** 221.

Guinea-pigs were sensitized to 2,4-dinitrochlorobenzene and croton oil and the appropriate lymph nodes removed and examined. No evidence was found that the regional lymph node plays any special role in the development of eczematous sensitization, but the results do not exclude the possibility. J. K.

HISTOCHEMICAL EVIDENCE FOR HUMAN ECCRINE SWEAT DUCT ACTIVITY. Walter C. Lobitz, jnr., John B. Holyoke and Doris Brophy. (1955) *Arch. Derm. Syph., Chicago,* **72,** 229.

The evidence indicates that the cells lining the sweat ducts are metabolically active, but what action they have on the final composition of sweat is not clear. J. K.

OCCURRENCE OF CATARACTS AND KERATOCONUS WITH ATOPIC DERMATITIS. Louis A. Brunsting, William B. Reed and Hugo L. Blair. (1955) *Arch. Derm., Syph., Chicago,* **72,** 237

Of 2784 patients with atopic dermatitis seen at the Mayo clinic from 1940–1953, 1158 were examined by slit lamp. Cataract was discovered in 136 patients, 57 of whom had no obvious evidence of cataract. Some of the subclinical cases showed no significant change over a period of years, while others showed intensification of the opacities with aggravation of the dermatitis.

Keratoconus was found in 6 patients with atopic dermatitis seen from 1940–1954, 3 of whom also had minor lenticular opacities. J. K.

MASTOCYTOSES EXCLUDING URTICARIA PIGMENTOSA: DIFFUSE MASTOCYTIC RETICULOSES. R. Degos. (1955) *Arch. belg. Derm. Syph.,* **11,** 10.

The author proposes to classify dermatoses characterized by mast cell proliferation as follows:

(1) Urticaria pigmentosa.

(2) Mastocytic tumours; small, well defined, brown in colour resembling fibromata or naevo-carcinomata.

(3) Bullous types, associated with other forms, especially nodular.

(4) Multinodular or papular types, non-pigmented though yellowish in colour, becoming turgescent on rubbing.

(5) Diffuse cutaneous forms characterized by dense diffuse thickening of the skin; the typical mastocytic reticulosis.

(6) Viscero-cutaneous forms found in infants and adults meriting the name of malignant mastocytic reticulosis.

All show yellowish or ivory-like, thickened skin of pasty, soft or elastic consistency. The natural folds of the skin are exaggerated and at first sight it looks lichenified. The surface is smooth or strewn with little elevations giving a shagreen appearance; it may be covered with actual nodules. Though it may be universal the sites of election are the axillae and the groins. J. K.

CORTICOTHERAPY IN THE TREATMENT OF CHRONIC GENERALISED ECZEMA IN THE AGED. J.-J. Meyer-de Schmid. (1955) *Arch. belg. Derm. Syph.,* **11,** 45.

The author has, during the past two years, changed his views on the value of cortisone in eczema in the aged. He now considers it effective and safe, even if given to outpatients. The following facts have been noted

(1) The dose should be small at first and gradually increased until control is achieved. He finds 40 to 150 mg. a day sufficient. The diet should be chloride free with the addition of 1 to 2 g. daily of potassium chloride.

(2) Once the effective dose is reached it can be gradually reduced, after a period varying from a few days to a few months, by steps of 5 mg. at a time. If any sign of relapse appears the dose should be increased.

(3) Other treatment, especially ACTH and testosterone, has not been necessary.

(4) No complications have occurred. Hospitalization has been kept to a minimum. Blood pressure and weight have remained satisfactory and there has been no occurrence of oedema.

(5) There has been no recurrence when treatment was stopped. J. K.